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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,245	06/24/2002	Johan - Valentin Kahl	GRUNP118	9295

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EXAMINER	
BARTON, JEFFREY THOMAS	
ART UNIT	**PAPER NUMBER**
1753	

DATE MAILED: 03/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,245	KAHL ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Barton	1753	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendment filed on 31 December 2004 does not place the application in condition for allowance.

Status of Objections and Rejections Pending Since the Office Action of 01 October 2004

2. All objections and rejections of claims 1-46 are withdrawn due to cancellation of the claims.

3. New claims 47-66 are rejected on the same grounds used for rejecting original claims 1-20.

4. New grounds are presented for the rejection of claims 67-81, which were necessitated by Applicants' amendment.

Prior Claim Rejections - 35 USC § 102

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 47, 50, 51, 55, 57, and 63 are rejected under 35 U.S.C. 102(e) as being anticipated by Boxer et al.

Addressing claim 47, Boxer et al disclose a method for electrophoretically separating particles, comprising: applying the particles to be separated on a substrate-

supported membrane such that the particles are mobile across the surface of the membrane (Column 20, lines 22-49); providing an electric field oriented along the membrane surface (Column 20, line 49-55); and using a substrate-supported membrane having a structured surface such that a force is acting on the particles that leads to movement depending on the length of the particle. (Column 19, lines 20-57)

Addressing claim 51, Boxer et al disclose the membrane comprising amphiphilic macromolecules (Column 7, lines 38-40)

Addressing claim 52, Boxer et al disclose the membrane comprising bilayers of charged lipids. (Column 22, lines 18-31)

Addressing claim 55, Boxer et al disclose using a structured substrate comprising ribs to support the membrane. (Figure 1, 28; Figures 2 and 5)

Addressing claim 57, Boxer et al disclose the height of the ribs being as low as a few nanometers. (Column 5, lines 59-61)

Addressing claim 63, Boxer et al disclose separation of nucleic acids and proteins. (Column 12, lines 12-21)

Prior Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al in view of Raguse et al.

Boxer et al disclose a method as described above in addressing claim 47. They also disclose their method being able to use membranes formed of any bilayer-forming amphiphile. (Column 7, lines 38-40)

Boxer et al do not explicitly disclose their method using lipids activated by PEG or DAX-Chol lipids for the membrane.

Raguse et al disclose preparation of lipid bilayer membranes using a polyethylene glycol head group. (Column 3, lines 25-38; Column 17, lines 30-34)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Boxer et al by using bilayers comprising lipids with polyethylene oxide head groups, as taught by Raguse et al, because Raguse et al teach their ability to form bilayers, and Boxer et al suggest the use of any bilayer-forming lipids in their method.

9. Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al and Raguse et al as applied to claim 48 above, and further in view of Bailey et al.

Boxer et al and Raguse et al disclose a combined method as described above in addressing claim 48.

Neither Boxer et al nor Raguse et al explicitly disclose their method using bilayers comprising cationic lipids.

Bailey et al disclose preparation of liposomes comprising bilayers including cationic lipids. (Abstract)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of Boxer et al and Raguse et al by using bilayers comprising cationic lipids, as taught by Bailey et al, because Bailey et al teach their ability to form bilayers, and Boxer et al suggest the use of any bilayer-forming lipids in their method.

10. Claims 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al in view of Allington.

Boxer et al disclose a method as described above in addressing claim 47. They also disclose the similarity of the separation characteristics of one embodiment of their invention to gel electrophoresis. (Column 19, lines 51-57)

Boxer et al do not explicitly disclose their method using a pulsed electric field (Claim 52), a time constant field superimposed on an alternating field (Claim 53), or the fields of claim 7 being superimposed in a crosswise manner. (Claim 54)

Allington discloses gel electrophoresis methods in which a pulsed electric field is used (Title, Abstract), and a perpendicular alternating field is superimposed on a constant field. (Page 15, lines 3-26)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Boxer et al by using pulsed electric fields or perpendicular superimposed alternating and constant electric fields, as taught by Allington, because Boxer et al disclosed that his method resembles gel electrophoresis

in size-based separations, and such pulsed fields would aid in separating larger macromolecules.

14. Claims 56 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al in view of Austin et al.

Boxer et al disclose a method as described above in addressing claims 9 and 26. They also disclose the ability of their preparation methods to provide features on the nanometer scale. (Column 11, lines 8-12)

Boxer et al do not explicitly disclose the preparation of substrates having structure periodicity of 2-200 nm.

Relevant to claim 56, Austin et al disclose a device suitable for electrophoretic fractionation, which has substrate structures having a periodicity as low as 10 nm. (Column 11, lines 23-27; Figures 3-4A)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Boxer et al by preparing structures in the substrate with periodicity as low as 10 nm, as taught by Austin et al, because Boxer suggested the ability to prepare structures on the nanometer scale, and it would provide the ability to separate smaller molecules.

Furthermore, regarding claim 59, it is obvious that upon migration and contact with a barrier such as those disclosed by Boxer et al or Austin et al, any molecule with a degree of asymmetry will be caused to rotate to some degree.

15. Claims 58, and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al in view of Wiktorowicz et al.

Boxer et al disclose methods as described above in addressing claims 47 and 55. They also disclose the similarity of the separation characteristics of one embodiment of their invention to gel electrophoresis. (Column 19, lines 51-57)

Boxer et al do not explicitly disclose their method using an electric field parallel to ribs on the substrate (Claim 58), nor do they disclose any pH gradients in their methods (Claims 64-66)

Wiktorowicz et al disclose electrophoresis methods (primarily gel, but open to others, as indicated by "separation medium" language) in which an electric field is applied parallel to ribs in the substrate. (Figures 3-5; Column 6, lines 39-50) They also disclose electrophoresis methods using pH gradients parallel to the electric field (Isoelectric focusing, Column 8, line 61 - Column 11, line 10) and perpendicular to the electric field (Second dimension after IEF or first dimension before IEF) (Column 15, lines 11-43)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Boxer et al by using an electric field parallel to ribs in the substrate, as taught by Wiktorowicz et al, it would allow analysis of multiple parallel samples in a single run.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Boxer et al by incorporating an immobilized pH gradient on a substrate surface in one dimension of a two-dimensional separation,

as taught by Wiktorowicz et al, because it would provide a useful prefractionation in the separation of complex mixtures.

16. Claims 60 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al in view of Groves et al.

Boxer et al disclose a method as described above in addressing claim 47. They also disclose exclusion areas, delineated by the bilayer barrier materials (Column 7, lines 12-19; Figure 1)

Boxer et al do not explicitly disclose collecting particles at the exclusion area upon application of an electric field prior to separation (Claim 60), nor do they disclose observing the separation by recording digitized image data of the separation and evaluating the data using a computer. (Claim 62)

Relevant to claim 60, Groves et al disclose the electrophoretic migration of proteins into "corrals" scratched into the substrate surface of a similar device. (Figure 5; Page 2720-2721)

Relevant to claim 62, Figure 4 shows recorded image data, further described by graph insets that were made by computer.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Boxer et al by concentrating analytes in exclusion areas on the substrate prior to analysis, as taught by Groves et al, because it would provide more effective separation, as in known stacking procedures.

It would also have been obvious to modify the method of Boxer et al by recording image data of the separations and evaluating the data by computer, as taught by Groves et al, because it would provide a complete and efficient means of evaluating the separation.

17. Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al and Groves et al as applied to claim 60 above, and further in view of Raguse et al.

Boxer et al and Groves et al disclose a combined method as described above in addressing claim 60. Boxer et al also disclose their method being able to use membranes formed of any bilayer-forming amphiphile. (Column 7, lines 38-40)

Neither Boxer et al nor Groves et al explicitly disclose their method using lipids activated by PEG or DAX-Chol lipids for the membrane.

Raguse et al disclose preparation of lipid bilayer membranes using a polyethylene glycol head group. (Column 3, lines 25-38; Column 17, lines 30-34)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of Boxer et al and Groves et al by using bilayers comprising lipids with polyethylene oxide head groups, as taught by Raguse et al, because Raguse et al teach their ability to form bilayers, and Boxer et al suggest the use of any bilayer-forming lipids in their method.

New Claim Rejections - 35 USC § 102

11. Claims 67-70, 72, and 75 are rejected under 35 U.S.C. 102(e) as being anticipated by Stowell et al.

Regarding claim 67, Stowell et al disclose a dried, substrate-supported membrane. (Column 5, lines 45-60)

Regarding claim 68, they use cationic lipids. (Column 5, lines 45-49)

Regarding claim 69, proteins are entrapped in the membranes. (Column 5, lines 62-67; Figure 3)

Regarding claim 70, the membranes comprise lipid bilayers (Figures)

Regarding claims 72 and 75, the substrates are made of glass. (Column 5, lines 29-34)

12. Claims 67, 69, 70, 72, 73, and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Peterson.

Regarding claim 67, Stowell et al disclose a dried, substrate-supported membrane. (Figure 1, membrane 7, support 6; Page 2, lines 12-17)

Regarding claim 69, the membranes comprise proteins. (Page 3, lines 7-15)

Regarding claim 70, the membranes comprise lipid bilayers (Page 3, lines 7-13)

Regarding claims 72, 73, and 75, the support is made of PTFE. (Page 3, lines 16-21)

New Claim Rejections - 35 USC § 103

13. Claims 67, 69-72, 75-78, 80, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Groves et al in view of Goodrich, Jr. et al.

Regarding claims 67, 69-72, and 75, Groves et al disclose lipid bilayer membranes comprising proteins that are supported on glass coverslips. (Pages 2717-2718 - Supported bilayers section) Non-fluid areas are provided by scratching with tweezers. (e.g. Page 2718, Membrane electrophoresis section, second sentence)

Regarding claim 76, Groves et al disclose a channel comprising this membrane and an electrode assembly. (Figure 2 - coverslip sandwich itself can be called a channel)

Regarding claim 77, this channel is 10 mm wide.

Regarding claim 78, the channel depth is disclosed as 10-50 microns. (Figure 2 caption)

Regarding claims 80 and 81, the electrodes pictured in Figure 2a are on the longitudinal ends of the channel, and extend longitudinally in the direction of the channel from either end.

Groves et al do not explicitly disclose drying the membrane.

Goodrich et al disclose a method of freeze-drying such lipid membranes for storage and later use. (Column 4, lines 46-61)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the devices of Groves et al by freeze-drying the membrane sandwiches for later use, as taught by Goodrich et al, because it would allow

a researcher to choose when to use a membrane, as opposed to needing to prepare a freshly prepared membrane for each experiment, and Goodrich et al teach the usefulness of the method in storing synthetic phospholipid membranes. (Column 4, lines 46-55)

14. Claims 67, 69, 70, and 72-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al in view of Goodrich, Jr. et al.

Regarding claims 67, 69, 70, 72, and 75, Boxer et al disclose lipid bilayer membranes comprising proteins that are supported on glass coverslips. (Column 7, lines 20-40)

Regarding claims 73 and 74, Boxer et al disclose the support comprising PMMA. (Column 10, lines 4-11)

Regarding claim 76, Boxer et al disclose a channel comprising this membrane and an electrode assembly. (e.g. Figure 5 - area between electrodes can be called a channel)

Regarding claim 77, the supports (and therefore channels) are disclosed as having dimensions as low as 5 mm per side. (Column 5, lines 41-43)

Regarding claim 78, the disclosed bilayer and aqueous film thickness would result in a channel of this depth. (Column 5, lines 50-64)

Regarding claim 79, Boxer et al disclose two-dimensional arrays of membrane sections, which could be called channels. (e.g. Figure 2, Column 8, lines 43-52)

Regarding claim 80, the electrodes pictured in Figure 5 are on the longitudinal ends of the channel.

Boxer et al do not explicitly disclose drying the membrane.

Goodrich et al disclose a method of freeze-drying such lipid membranes for storage and later use. (Column 4, lines 46-61)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the devices of Boxer et al by freeze-drying the membrane sandwiches for later use, as taught by Goodrich et al, because it would allow a researcher to choose when to use a membrane, as opposed to needing to prepare a freshly prepared membrane for each experiment, and Goodrich et al teach the usefulness of the method in storing synthetic phospholipid membranes. (Column 4, lines 46-55)

15. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Groves et al and Goodrich, Jr. et al as applied to claim 67 above, and further in view of Bailey et al.

Groves et al and Goodrich et al disclose a combination as described above in addressing claim 67.

Neither Groves et al nor Goodrich et al explicitly disclose a membrane comprising cationic lipids.

Bailey et al disclose preparation of liposomes comprising bilayers including cationic lipids. (Abstract)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of Boxer et al and Goodrich et al by using bilayers comprising cationic lipids, as taught by Bailey et al, because Bailey et al teach their ability to form bilayers and the function of the cationic lipid in promoting liposome fusion.

16. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Boxer et al and Goodrich, Jr. et al as applied to claim 67 above, and further in view of Bailey et al.

The reasoning for this rejection parallels that given above in paragraph 9.

Response to Arguments

17. Applicant's arguments filed 31 December 2004 have been fully considered but they are not persuasive.

Regarding the Boxer et al reference, Applicants argue that Boxer et al teach sorting of molecules that have always been attached to the membrane or incorporated into the membrane, not the application of molecules onto the surface of the membrane such that they are mobile. (Amendment Page 13, 1st paragraph) In fact, Boxer et al teach application of molecules to the surface of an already-formed membrane (e.g. Column 13, lines 36-52), and such materials are indeed mobile across the surface of the membrane. (e.g. Column 18, line 64 - Column 19, line 19)

Also regarding the Boxer et al reference, Applicants argue that Boxer et al do not disclose modifying strength or direction of the electric field. Examiner agrees with this, but the wording of the claim makes these limitations optional. Applicants further argue that Boxer et al do not disclose a membrane with a structured surface. (Amendment Page 13, 2nd and 3rd paragraphs) Part of the arguments presented read: ". . . [the bilayer barrier] regions are intended solely to interrupt the membrane at specific parts." (Page 13, 3rd paragraph, 1st sentence) The Examiner considers such interruptions, if occurring in a regular pattern, to read on the word "patterned".

As can be seen in the embodiment of Figure 5 of Boxer et al, the entire membrane (i.e. interior and exterior surfaces) is physically patterned by the bilayer-barrier surface regions 78, which had been disclosed as ranging in height up to a few microns. (Column 5, lines 59-64) The disclosed sorting method (Column 19, lines 41-50) relies on progressively narrower physical gaps, which indicates, for surface-bound analytes, that the surface must physically reflect this pattern. This is further illustrated in Figure 1, which shows the patterning extending through the entire membrane - including the surface - due to the barrier layer 26. The Examiner maintains that this reads on the limitation to a patterned surface.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Jeffrey Barton, whose telephone number is (571) 272-1307. The examiner can normally be reached Monday-Friday from 8:30 am – 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam Nguyen, can be reached at (571) 272-1342. The fax number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

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JTB
February 22, 2005

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